

Differential diagnosis of bipolar disorder in children and adolescents

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Issues complicating the differential diagnosis of bipolar disorder in young people are discussed. They include: a) the subtype of bipolar disorder being considered; b) the person's age and stage of development; c) whether one views bipolar disorder more conservatively, requiring clear episodes that mark a distinct change from premorbid levels of function, or more liberally, focusing for instance on severe irritability/explosive outbursts as the mood change; d) who is reporting manic symptoms, and whether symptoms are past and must be recalled or current and more likely to be observed; e) impact of family history. The diagnosis of mania/bipolar I disorder may not become clear for a number of years. This is an impairing disorder, but so are the conditions from which it must be distinguished. Family history may increase the odds that certain symptoms/behaviors are manifestations of bipolar disorder but it does not make the diagnosis. Until there are biomarkers that can confirm the diagnosis, and treatments unique to the condition, it is wise to make a diagnosis of bipolar disorder in children and adolescents provisionally and keep an open mind to the likelihood that revisions may be necessary.

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At least five issues complicate the differential diagnosis of bipolar disorder in young people: a) the subtype of bipolar disorder being considered (i.e., the differential diagnosis of mania vs. that of depression; the differential diagnosis of bipolar I disorder vs. that of bipolar disorder not otherwise specified (NOS)); b) the child's age and stage of development; c) whether one views bipolar disorder more conservatively, requiring clear episodes that mark a distinct change from premorbid levels of function, or more liberally, focusing for instance on severe irritability/explosive outbursts as the mood change; d) who is reporting manic symptoms, and whether symptoms are past and must be recalled or current and more likely to be observed; e) the utility of family history in making a diagnosis.

Children and adolescents are not necessarily good reporters about events in time, or may not understand such abstract concepts as euphoria and racing thoughts. Parents may not be aware of or may misinterpret their child's internal state. Children spend almost half their waking life in school, so that, if a child is experiencing a prevailing mood most of the day every day, a teacher should be able to notice a behavioral change, whether or not he/she recognizes symptoms as being manic or something else (1).

This review focuses primarily on mania, and distinguishes adolescents from children. We try to address broad vs. narrow approaches to diagnosis, and we discuss the implications of informant variance for diagnosis.

MANIA IN POST-PUBERTAL YOUTHS

Jeffrey, who was 14 when first evaluated, was described as an energetic, motivated, creative and gregarious adolescent, who involved himself in multiple activities but completed them successfully. He was conscientious and respectful, and

had many interests. Over the course of a few months, however, he developed attention problems, began using the neighbors' swimming pool at 2 am without their permission, tried to call President Bush to give him advice about invading Iraq, and became testy and oppositional with parents when they tried to get him to get a decent night's sleep. Following this period, which lasted several weeks, Jeffrey became bed-ridden with fatigue, disinterested in friends or activities, and almost stopped eating. He felt very depressed. Further interview elicited other symptoms of mania with no past history of depression. Consultation was sought about whether this was "adolescence" or psychopathology. Complicating matters, he had sustained a head injury playing football and, although he did not lose consciousness, there was some question about whether his behavior, which began several weeks later, was related to the head trauma.

While Jeffrey appears to have experienced a fairly classic manic episode, several issues need further evaluation:

- How much do Jeffrey's behavior encompass a clear departure from his prior "hyperthymic temperament"? (2). A hyperthymic person is habitually upbeat and exuberant, articulate, jocular, overoptimistic, uninhibited, carefree, energetic and full of improvident plans, versatile with broad interests, overinvolved and even meddlesome. That certainly characterized Jeffrey. Had he crossed the boundary into a hypomanic or manic episode? The boundary would have been clearer had Jeffrey been a quiet, unassuming character prior to going into what appeared to be his overdrive, but his impairment and subsequent depression were not consistent with temperament alone.
- Was Jeffrey's head injury relevant? There are case reports noting the association between traumatic brain injury and mania (3). There is also a condition called "personality change following traumatic brain injury" (4), referring to

a disinhibited state that was called organic affective disorder in earlier DSMs.

- Is there any evidence that Jeffrey is abusing substances? New onset mood symptoms in teenagers warrant questions about drug and alcohol abuse and dependence (5). Teens abusing marijuana, alcohol, or other drugs, may develop psychosis and/or mood symptoms. While a positive toxicology screen helps document drug involvement, negative drug screens do not rule out substance abuse. Furthermore, symptoms of mania may continue for weeks after the patient is drug free. It is often difficult to disentangle whether drug abuse has precipitated a mood episode that otherwise would not have occurred, has hastened its onset, perpetuates a mood problem that might otherwise have subsided, or is irrelevant (6).

Between 11% and 27% of teens hospitalized for a first psychotic episode have a diagnosis of bipolar I disorder at least initially (7). It is often very difficult, however, to be definitive in diagnosis with the first episode, because symptoms may be confusing or may change over time.

For instance, Dennis was 16 when, over the course of 3 days, he stopped sleeping, felt he could control the world, wrote letters that everything had a purpose and was interconnected, including the German swastika, the pyramids and the peace symbol. He was physically restless and hyperverbal. He became increasingly paranoid, feeling his psychiatrist wanted to hurt him. Over the next 6 months, with treatment (antipsychotic and lithium), his affective symptoms remitted, but he developed thought broadcasting and referential thinking which never remitted. Ten years later, he was diagnosed with schizoaffective disorder because of his chronic thought disorder and unremitting psychotic symptoms. His medications appeared to attenuate his mood symptoms, but not his negative symptoms.

Although almost 70% of first episode psychotic manic subjects retained a bipolar or probable bipolar diagnosis at 10 years following their initial episode (8), predictors of worse outcome and change in diagnosis were Schneiderian symptoms at baseline, and poor premorbid functioning. Other harbingers of poor outcome were depressive phenomenology, childhood psychopathology, and younger age at first hospitalization (9).

MANIA IN CHILDREN

Mania in children before the age of 10 is more contentious than mania in adolescents (10). In applying DSM-IV-TR bipolar disorder criteria to children, several modifications have been proposed in order to fit the symptom profile of mania to symptoms more common in younger children. Unresolved is whether these children grow up to manifest clear episodes of mania and depression like Jeffrey (acute onset of mania, discrete episodes, little comorbidity) vs. ongoing dysregulated mood with depression – similar to subjects in the System-

atic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (11) – vs. some other outcome, including maturity with no further episodes (12).

An insidious problem with the diagnosis of early-onset bipolar disorder is different interpretation of the criteria. There is little disagreement on classic cases of mania, where onset is clear and manic symptoms co-occur that are easily distinguished from other psychopathology. In other less “classic” cases, however, there is considerably greater disagreement (13). Reliability can be achieved easily enough within groups, but that does not guarantee reliability across groups.

According to DSM-IV-TR, a manic episode is identified as a “distinct period” of specific and co-occurring symptoms. Unfortunately, “distinct period” has not been consistently operationalized (14). Thus, the criteria for mania will be undergoing some modifications in the DSM-5 (see www.dsm5.org). As noted in the rationale for these changes, “the question of what constitutes an episode has been the subject of some controversy and confusion, especially in the child psychiatry literature”. In the view of the Mood Disorders Work Group, the wording of the DSM-IV criteria for mania and hypomania may have contributed to that confusion. The proposed change is therefore a clarification whose goal would be to ensure that diagnostic practices remain consistent with both the intention of previous iterations of the DSM and across the developmental spectrum. Thus, criterion A is expected to read: “a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and *present most of the day, nearly every day* (or any duration if hospitalization is necessary)”.

The conceptualization of symptoms is important to the discussion of the differential diagnosis of mania. While depressive symptoms have been recognized as being different from a depressive episode, or “clinical depression”, there has been little appreciation that manic symptoms may occur outside of a manic episode. Originally highlighted in a community study in 1988 (15), a number of studies since have confirmed the fact that manic symptoms occur much more frequently than a manic episode, are significantly impairing, but cut across many conditions (16,17). Without the clarification of a distinct episode, a period with an onset and an offset that is different from one’s “usual behavior”, and without information in young children about what “usual behavior is”, it is very difficult to distinguish mania from other childhood conditions in which irritability and agitation also occur.

Attention-deficit/hyperactivity disorder (ADHD) is the condition most often confused with mania in children (18). There is considerable symptom overlap (both conditions have notable distractibility, impulsivity, hyperactivity, rapid and overproductive speech) (19). However, children with manic symptoms have more than uncomplicated ADHD. They invariably meet criteria for other disorders (comorbidities) and are considered more impaired (20,21). Interestingly, when children with manic symptoms are matched with ADHD children with similar comorbidities, differences between

them evaporate (22,23). The diagnostic question becomes whether children with manic symptoms have bipolar disorder and ADHD or whether they have ADHD with high levels of emotionality and/or oppositional defiance.

Emotionality/oppositional defiance in ADHD is noted in the DSM-III/IV text among “associated symptoms”. The DSM-IV-TR text states that the emotionality component includes low frustration tolerance/irritability, temper outbursts, mood lability, dysphoria and low self-esteem. These symptoms clearly reflect a mood dimension. The emotionality component maps onto both inattentive and hyperactive dimensions of ADHD. The inattentive ADHD symptoms may be primarily associated with breakdowns in the regulation side, whereas hyperactivity-impulsive ADHD symptoms may be associated with breakdown in the emotionality side (24). What is evident is that children with either bipolar disorder or ADHD and emotionality are more clearly impaired cross-sectionally and longitudinally than children with uncomplicated ADHD (20,25).

ADHD and bipolar disorder frequently co-occur. The recently published Longitudinal Assessment of Manic Symptoms study (16) most carefully dissects the question of ADHD and bipolar disorder (20). The investigators compared 6-12 year old children whose parents endorsed manic symptoms on an instrument called the General Behavior Inventory (26) (n=621) with a lower scoring group (n=86). Of the total 707 children, the vast majority (59.5%) had ADHD without a bipolar spectrum disorder, 6.4% had a bipolar spectrum disorder without ADHD, 16.5% had both, and 17.5% had neither. Bipolar spectrum disorder was equally divided into bipolar I disorder and bipolar disorder NOS (with few having bipolar II disorder). Similar to prior studies (1,15), most children with manic symptoms did not have bipolar spectrum disorder. Of the 162 children who had bipolar spectrum disorder, most (72.2%) had co-occurring ADHD. Parent ratings revealed that this combination produced more symptoms than either condition alone. Diagnosis was made with the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS-PL, 27) and, though the authors do not specify, one assumes it was based mostly on parent information, since teachers often disagreed (20). Nevertheless, considerable care was taken to distinguish chronic symptoms from acute or fluctuating ones and it is precisely that approach which is needed to help distinguish mania from ADHD from the co-occurrence of the two conditions.

Apart from taking a history which establishes that an episode has taken place, further vetting of possibly overlapping symptoms is necessary. Symptoms that lend themselves to confusion between mania and ADHD include:

- The silly, disinhibited behavior of a child with ADHD trying to be funny and not knowing when to quit vs. someone with an elated mood.
- Impulsivity vs. pleasure-seeking without heeding consequences.
- Resistance to bedtime vs. a reduced need for sleep.

- Exacerbation of subthreshold ADHD symptoms because of increased late elementary or middle school demands vs. the start of a mood disorder.
- Progression of ADHD symptoms to include more oppositional/explosive/conduct disordered behavior in the context of family, school and/or peer difficulties.
- Pragmatic, distracted or odd language seen in children who have language disorders as part of ADHD or an autism spectrum disorder vs. the flight of ideas/thought disorder of mania.
- “Hallucinations” seen in a very anxious child vs. mood incongruent symptoms of mania.

Children with autism spectrum disorders may be confused with children with mania because of their emotion regulation problems (28). Not only do these children have hyperactivity and impulsivity, but their pragmatic language difficulties can look like a thought disorder to clinicians who are not versed in the difference (29). As in the case of ADHD, however, a good history should help distinguish which symptoms are chronic and which are manifestations of a new condition. Interestingly, although autism and bipolar disorder (including more classic episodic bipolar disorder) have been often associated (30), children with known pervasive developmental disorder are almost always excluded in formal research studies.

MOOD DYSREGULATION

Lynda, described elsewhere (13), was 11 and presented with what her parents called “mood swings”, i.e. frequent explosive outbursts when she was frustrated over anything, no matter how trivial. She had a history since toddlerhood of ADHD, which never completely remitted with stimulant medication. By 5th grade, she had become very irritable, disobedient, nasty to her parents and dismissive of their concerns about her poor school performance, grandiosely feeling she needed no education. She viewed pornographic sites on the computer and stayed up late at night allegedly “on line with friends”. She was behind academically and unpopular with classmates. She was not explosive in school, but ADHD symptoms were evident. Her parents endorsed manic-like symptoms during interview. Lynda herself described dysphoria, irritability, trouble concentrating, low self-esteem, and occasional suicidal ideation. In addition, there was considerable strife at home, though no actual domestic violence. Lynda’s differential diagnosis using DSM-IV criteria would include ADHD and emerging oppositional defiant and possible conduct disorder, major depressive disorder, an adjustment disorder secondary to increasing failure socially, academically and at home, and an episode of mixed mania.

Mood dysregulation/lability is increasingly recognized as an important component of a number of conditions (31). The lay public, in fact, uses the term “bipolar” to characterize “mood swings”, i.e., abrupt changes in mood that seem inex-

plicable to the observer. The reference is to a switch to a negative mood, the essence of irritability. In the throes of a manic episode, children and adults are often irritable. What has proved controversial is the question of whether children who become severely explosive have mania or whether this behavior, like irritability in general, cuts across all the conditions in which irritability is a prominent symptom (like depression, anxiety, schizophrenia, etc.) (32).

DEPRESSIVE AND ANXIETY DISORDERS

Irritability, of course, is an important symptom not only in mania, but also in depression (both major depressive disorder and dysthymia) and anxiety disorders (including post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, separation and generalized anxiety disorders). As with ADHD, the question is often not an “either or”, but a “both”. The distinction between mixed mania or rapid cycling and an agitated depression is especially difficult. In fact, some consider agitated depression as part of the bipolar spectrum (33). Longitudinal follow-up (34) and follow-back (35) data suggest that a predominantly depressive course in children with bipolar spectrum disorders is more chronic and treatment refractory than a predominantly manic course (9). The question in the childhood group followed prospectively will be how many either “outgrow” their manic symptoms and remain depressed (36) or even remit (12).

Irritability and hyperarousal are also symptoms of anxiety. Anxiety disorders are a common bipolar comorbidity in adults and youth. In adults, anxiety symptoms decreased the probability of recovering from a depressive episode of bipolar disorder, increased time to recovery, and increased the likelihood of relapse (37). In children, anxiety disorder usually precedes the onset of mania, in which case, a *bona fide* manic episode would be comorbid. Without a prior history of anxiety, it is quite possible that the symptoms of anxiety are part of the manic episode and not truly comorbid (38). In children and adolescents, anxiety appears more often associated with bipolar II disorder. Those with bipolar II disorder and anxiety had more concurrent depressive symptoms, longer and more severe depressive episodes, and a greater family history of depression than those without comorbid anxiety (38).

DISRUPTIVE MOOD DYSREGULATION DISORDER

In an effort to better understand the similarities and differences between chronic, severe irritability and more classic, episodic bipolar disorder, Leibenluft and the National Institute of Mental Health (NIMH) Intramural Program on Mood Disorders have defined a condition called “severe mood dysregulation (SMD)” (32). This is characterized by chronic irritability with frequent explosive outbursts not better diagnosed as mania, schizophrenia or schizophrenia spectrum

disorder, pervasive developmental disorder, post-traumatic stress disorder, substance abuse, a medical or neurological condition. In a sample of 146 children, 75% in fact had comorbid ADHD and oppositional defiant disorder, and over half (58%) had at least a lifetime anxiety disorder. Although no actual follow-up studies of children with SMD have been done, extrapolated data (39-41) suggest that depression underlies these behaviors. It appears that the DSM-5 Mood Disorders Work Group will use the data gathered from this sample to add a condition to the manual as a mood disorder, and the condition will be called disruptive mood dysregulation disorder (DMDD) (see www.dsm5.org).

DMDD should be readily distinguished from mania because of the absence of episodes. In addition, the condition is defined as starting after age 6 (to keep tempestuous toddlers and preschoolers from being given the diagnosis) and before age 10 (to indicate it is a childhood disorder). It is chronic (i.e. symptoms have lasted for at least a year) to hopefully keep children who are responding to acute stressors, and who could be classified as having an adjustment disorder with disturbance of conduct or mood, from getting the DMDD diagnosis. DMDD, if the diagnosis is appropriately used, is severe and disabling (31).

DMDD’s biggest diagnostic problem will be that irritability and explosive outbursts occur with many known conditions (42). Children who present with rage outbursts (regardless of whether or not they have chronic irritability) find their way into emergency rooms, psychiatric and residential facilities and special education. They require a useful diagnosis that will allow quantification, suggest a treatment alternative and allow for insurance reimbursement. The usual diagnostic home for children with rage outbursts has been oppositional defiant and conduct disorder, neither of which are considered reimbursable because they are regarded as “parenting” or “social” problems. The absence of a valid and useful way of codifying rage outbursts has led to a misuse of the bipolar disorder diagnosis and has prevented us from understanding the seriousness of these outbursts (43).

There is a question of whether rage outbursts represent a difference of degree or kind from the tantrums of younger children (44,45). Interestingly, their structure is similar, but the duration is longer (at least 20 minutes rather than 5 minutes), and what the child does during the tantrum is worse (kicking, hitting, throwing, spitting) in part because a child or adolescent of 7-17 is bigger and can inflict more damage than a seriously disturbed toddler. There are no data to suggest these outbursts change with diagnosis (i.e., rage outbursts that occur during a panic attack look similar to those that occur during a manic episode, oppositional defiant disorder, depression, etc.) (46). Many clinicians are appropriately concerned that this “diagnosis” will be as misused as “bipolar disorder” (43). This could be avoided if the diagnostic rules are followed, and if “explosive outbursts” were to be used as a modifier to any condition in which they occur, much as catatonia is being proposed to modify a variety of disorders. For instance, a diagnosis of ADHD with explosive

outbursts as a modifier would allow the basic condition to be identified as well as the outbursts which are what is leading to the higher level of treatment.

INFORMANT VARIANCE

At a minimum, diagnosis in child and adolescent psychiatry requires interviewing the parent/caregiver and the child/adolescent. In the case of behavior disorders, like ADHD, teacher information is important. Unfortunately, agreement between informants is modest at best and kappa agreement between parent and child on mania and depression symptoms has been generally less than 0.2 when it was reported. Nevertheless, Biederman et al (47) found that both parent and child endorsed manic symptoms in 62.7% of cases diagnosed with mania, and Tillman et al (48) found that 49.5% of their sample agreed on manic symptoms.

However, Tillman's study reported that rates of agreement were highest for ADHD type symptoms (80% for rapid speech, 91.4% for increased energy, 85.9% for motor hyperactivity), 75.8% for irritable mood, and considerably lower for other manic symptoms (42.2% for elevated mood, 32.5% for grandiosity, 35.8% for flight of ideas, 34.4% for disinhibited behavior, 16.2% for decreased need for sleep, and 21.4% for psychosis). Furthermore, for the mania specific symptoms, child endorsements were much lower than parent endorsements. It is easy to see why there might be disagreement about whether children so diagnosed have mania vs. ADHD, since drawing conclusions about a child's internal state rests solely on parent interpretation.

Corroboration of a child's manic behavior by sources other than parents has not been a major thrust of research in bipolar disorder. Correlations between parents and teachers, where they have been obtained, are around $r = 0.3$ (49). Carlson and Blader (1) reported that, where parents and teachers agreed about high rates of manic symptoms (as obtained from the Child Mania Rating Scale (CMRS, 50)), logistic regression indicated 10-fold greater odds of children being diagnosed with externalizing disorders (ADHD, oppositional defiant disorder, conduct disorder, or any combination of these). Children with bipolar spectrum disorder were also more likely to have concordant parent/teacher ratings. By contrast, children with internalizing disorders (anxiety and depressive disorders) were 3.7 times more likely to have discordant parent and teacher CMRS ratings. In this study, however, diagnosis was made with a best estimate procedure using parent, child, teacher and testing information rather than only a semi-structured interview. Further information is needed to explain why a condition that is severe, and lasts days to weeks, is observed by parents and not teachers.

FAMILY HISTORY

Bipolar disorder clearly has a genetic component (51). An

old meta-analysis (52) reported that bipolar offspring are at 2.7 times higher risk to develop a psychiatric disorder and 4 times higher risk to develop a mood disorder compared to offspring of healthy parents. Recent studies report similar findings (53). Interestingly, however, rates of general psychopathology are much higher than rates of bipolar I disorder. Hillegers et al (54), for instance, found that, by age 21, 3% of a Dutch high-risk sample had bipolar I disorder, 10% had bipolar spectrum disorder, but 59% had psychopathology in general. Although high-risk children with mood symptoms are at higher risk than those without to develop bipolar disorder as adults, they are also at higher risk to develop a host of other conditions (55).

Many high risk studies compare bipolar parents' offspring with those of non-psychiatric controls, which underscores differences in risk. However, children who present clinically often have families with all sorts of other disorders such as ADHD, autism, learning disabilities, other mood disorders, and schizophrenia. There is some suggestion that offspring of lithium responding parents have a less complicated course than those of non-lithium responding parents (56), which might help with treatment decisions if the diagnosis of bipolar I disorder is made. However, the presence of the parental condition does not make a diagnosis in the child.

Finally, the age of risk for bipolar disorder is a long one. A population-based Danish sample confined to studying offspring of parents hospitalized with bipolar disorder found that rates through age 53 for the offspring of one parent with bipolar disorder was 4.4% compared to 0.48% with no parent with bipolar disorder. The rate before age 20 was negligible (57).

The conclusion to be drawn from this information is that, although family history can raise the index of suspicion about bipolar disorder, it cannot make a diagnosis, especially if the other diagnostic components of the condition in the child are absent.

CONCLUSIONS

Although mania/bipolar I disorder often has its onset in youth, the diagnosis may not become clear for a number of years. It is a complex and disabling condition, but so are the conditions from which it must be distinguished. Psychosis, substance abuse and agitated unipolar depression pose the greatest problems in differential diagnosis in teens. Disorders of executive function do so in children. Multiple informants increase diagnostic accuracy, though one must sort out differences in informant reports across parent, child and teacher. Positive family history may increase the odds that certain symptoms/behaviors are manifestations of bipolar disorder, but it does not make the diagnosis. Furthermore, complex children often come from complex families.

Until there are biomarkers that can confirm the diagnosis, and treatments unique to the condition, it is wise to make a diagnosis of bipolar disorder in children provisionally and

keep an open mind to the likelihood that revisions may be necessary (58). Stating that a child unequivocally has a lifetime disorder requires more evidence than we have.

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